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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,245	FEIFEL, DAVID	
	Examiner	Art Unit	
	ADITI DUTT	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-18,22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. The amendment filed on 16 February 2011 has been entered into the record and has been fully considered.

2. Claims 15-18, 22, and 24-26, drawn to a method for increasing sensorimotor gating or inhibiting serotonin-2A and/or alpha-1 receptor mediated neural function by administration of neurotensin agonist to a subject, are being considered for examination in the instant application.

Response to Amendment

Claim objection/rejections maintained

Priority

3. Applicant argues that all priority documents and the present application discloses that NT agonists are useful in the claimed method and one of skill in the art would recognize the family of molecules being referred to at the time the provisional application 60/431937 was filed.

4. Applicant's arguments are fully considered but not found to be persuasive for reasons provided in the previous Office Action dated 8/16/2010 (paras 6, 7). Except for PD149163, all other NT agonists as listed in claims 15, 16 and 24 are not disclosed in the '937 application. The provisional application also does not teach the limitations of claim 17 and 18. Additionally, even though Applicant argues that the family of NT agonists would be recognized, therefore, all species would be known to be useful in the

claimed method at the time of invention, is not persuasive, because some of the agonists listed in the instant claims (e.g. NT69L) were not effective in reversing DOI effects, in other words the '937 disclosure does not enable the use of NT69L for the instant method. Based on the above facts, '937 application does not have the invention as instantly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The rejection of claims 15-16, 18, 22, 24 and 26, under 35 U.S.C. 103(a) as being unpatentable over Wettstein et al., (1999) and Vollenweider et al (1998); in view of Bowden (2001); and further in view of Perry et al. (2001), is applied to the amended claims for reasons of record in the Office Action dated 16 August 2010.

6. Wettstein et al teach the selectivity of action of atypical antipsychotic drugs (e.g. NT agonists or NT1) as antagonists of the behavioral effects produced by the psychotropic serotonin receptor agonist DOI following intraperitoneal (i.p.) administration of DOI and NT1 in rats. The reference teaches that NT1 antagonizes and attenuates the behavioral effects of DOI like head and body shakes, fore paw tapping, skin jerks etc., in a dose dependent manner (page 536, para 2; figure 4; abstract; page 540, para 1). Since DOI is a hallucinogen producing a clinical state similar to psychosis of schizophrenia, DOI is a psychoactive compound (page 539, para 2). Because DOI is a

serotonin receptor agonist and because NT1 administration antagonizes the antipsychotic effect of DOI, NT1 inhibits serotonin-2A mediated neurotransmission.

7. Wettstein et al. do not explicitly state the association of PPI deficits and 5-HT2A transmission. Wettstein et al. also do not teach the administration of NT1 in a human subject and the association of psychosis with bipolar disorder, anxiety or depression.

8. Vollenweider et al teach that psychotic disorders have the 5-HT2A receptor changes and PPI deficits, and that serotonergic hyperactivity results in such disorders. The reference also teaches that the 5-HT2A agonist DOI disrupts the PPI in rats (page 3901, col 2, para 1).

9. Wettstein et al do not teach the association of psychosis with bipolar disorder, anxiety or depression in humans.

10. Bowden teaches that bipolar disorder, depression disorder, anxiety disorders and schizophrenia are overlapping disorders in humans that have psychosis as a common feature (page 54, col 2, para 1; col 3).

11. Bowden does not teach the association of PPI deficits with the claimed disorders in humans.

12. Perry et al. teach that sensorimotor gating deficits as assessed by significantly lower PPI and habituation of the human startle response is observed in bipolar disorder patients (Abstract).

13. It would have therefore, been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the use of NT1 for reversing the effects of DOI induced psychotic behavior and PPI deficits in rats as taught by Wettstein et al., and Vollenweider et al. by administering NT1 to a bipolar disorder human subject to increase PPI and thereby increase sensorimotor gating in view of Bowden and Perry

et al. The person of ordinary skill in the art would have been motivated to use the NT agonist NT1 in human subjects as this compound can reverse all effects of DOI and therefore, prove to be an atypical antipsychotic (by reversing serotonin-2A transmission) in clinical development (Wettstein et al. page 540, para 1), and because DOI model was used for the screening of atypical antipsychotic drugs functioning via serotonin-2A receptors. Additionally, increase in head and body shakes in rats, corresponds to anxiety and depression disorder in humans (see for example, Benjamin et al, Drug Dev Res 26, 287-297, 1992; abstract). The person of ordinary skill in the art would have also been motivated to use serotonin-2A transmission inhibitors because typical antipsychotic agents (primarily reversing dopamine neurotransmission) are known to result in debilitating side-effects like motor control disabilities. Therefore, as Wettstein et al. indicate "research emphasis has been placed on discovering drugs that better treat the disease while having side-effect profiles much improved over the conventional compounds" (page 534, para 1). The person of ordinary skill in the art would have expected success as the development of atypical antipsychotics antagonizing the serotoninergic transmission for obtaining increased efficacy with decreased side effects was a continuing effort in the medical and pharmaceutical community at the time the invention was made.

Applicant's Remarks:

14. Applicant argues that Wettstein et al do not teach the selectivity of atypical antipsychotic drugs as antagonists of the serotonin agonist DOI induced behavioral effects. Applicant asserts that the effect produced by NT1 is not necessarily via blocking serotonin-2A function, i.e. NT1 is not an atypical antipsychotic. Applicant supports this

contention on the basis of Wettstein findings that the DOI reversal effects were also elicited by typical antipsychotics – haloperidol and other drugs like morphine that do not block serotonin-2A receptors. Applicant further states that "DOI induced prepulse inhibition (PPI) is more selectively reversed by drugs that block serotonin-2A function". Applicant argues that although Wettstein teaches that many drugs such as haloperidol reverse the DOI induced body shakes, forepaw tapping and skin jerks, haloperidol was not shown to be effective in correcting DOI-induced PPI disruption (Padich et al, abstract; Varty et al, abstract –cited by Applicant on page 6, para 2 of Remarks). Applicant therefore, alleges that the Patent Office does not have support for stating that Wettstein teaches that NT1 is necessarily blocking serotonin-2A receptor neurotransmission. Applicant further alleges that the teaching of Vollenweider, Bowden and Perry do not correct the deficiency of Wettstein teaching, as none of the references teach that NT agonists block 5-HT2A receptor function. Applicant also alleges that bipolar disorder, depression disorder and anxiety disorder are mood disorders, as these are not categorized as psychotic disorders in the Diagnostic and Statistical Manual of Mental Disorders. Because the claimed disorders are not psychotic disorders, Applicant concludes that there would be no motivation for the skilled artisan to combine the references.

15. Applicant's arguments are fully considered, however, are not found to be persuasive. The claims are directed to administering NT1 agonist to a subject having a bipolar disorder, an anxiety disorder or a depression disorder to improve the symptoms of said disorder/s, wherein the NT agonists inhibit serotonin-2A neurotransmission. Please note that the claims only require that the disorder be associated with serotonin-2A mediated neurotransmission, and that NT agonists improve the said disorder upon

administration to said subject. The limitation "wherein the NT agonist inhibits serotonin-2A mediated neurotransmission" clause at the end of claims 15, 16 and 24 recites a result of the method, but not a step that is to be performed by the artisan. Upon performing the steps of administering NT agonist to the recited patient population and improving symptoms of the said disorders, one will necessarily have inhibited serotonin-2A mediated neurotransmission.

16. Applicant's argument that NT1 does not necessarily block serotonin-2A function, simply because some of the other drugs in the experiment are known not to block serotonin is not persuasive. Applicant is picking on drugs like haloperidol that essentially act via the dopaminergic pathway. However, the reference also has serotoninergic compounds (M100907, a serotonin-2A antagonist) that clearly inhibit serotonin-2A mediated neurotransmission. DOI is a well-known serotonin-2A receptor agonist that induces behavioral changes e.g. head and body shakes that correspond to depression and anxiety disorders in humans. DOI also reduces PPI. Because DOI is a serotonin-2A receptor agonist, the effect of DOI is mediated via serotonin-2A neurotransmission. The fact that NT1 is blocking the behavioral effects produced by DOI, implies that NT1 is blocking the serotonin-2A neurotransmission induced by DOI even though the reference does not clearly state so. Applicant is alleging that Wettstein states that the compounds in the experiment may exert their action via different mechanism. This may be true, however, the reference does not categorically state that NT1 is not acting via serotonin-2A pathway. On the contrary, the reference is trying to develop antipsychotic agents that antagonize serotonin-2A function/activity by blocking DOI (Wettstein, conclusion).

17. Still further DOI is a hallucinogen and is useful in developing antipsychotic compounds for treating illnesses like schizophrenia. It is well-known that a subject

afflicted with schizophrenia has depression, anxiety or bipolar disorder (see for example Whitehead et al. Cochrane Collab., pages 1-35, 2010, page 1, background). Additionally Wettstein and the instant specification teach the developing of atypical antipsychotics that correspond to antagonists of serotonin-2A inhibition or DOI induction. Therefore, it is implied that depression, anxiety or bipolar disorder disorders coexist with schizophrenia and the disorders are overlapping in humans that have psychosis as a common feature as taught by Bowden and indicated in the previous Office Action (para 14).

18. It is also known that drugs for treating schizophrenia having a depression disorder for example, will overlap with drugs for treating depression without schizophrenia, as in schizoaffective disorder (Whitehead et al. 2010). Lastly even though Applicant points out that depression, anxiety or bipolar disorder are largely categorized as mood disorders, and that psychosis may not be the core feature of these disorders, Applicant still admits that psychosis occurs in some cases of manic episodes (a feature of bipolar disorder). Likewise psychosis though rare, nonetheless occurs in anxiety and depression disorders, and can also occur in cases of co-existing conditions (Applicant's remarks, pages 7-8).

19. Furthermore, Applicant's allegation that some of the drugs used by Wettstein reversed DOI induced behavior but not DOI induced PPI disruption, a characteristic typical for drugs that block serotonin-2A receptors is not persuasive, primarily because PPI disruption is not recited in the instant claims. If Applicant is indicating towards the limitation "increasing sensorimotor gating" as corresponding to PPI disruption, it is noted that such limitation in the preamble of claim 15, is indicating an intended use of the claimed method steps and does not receive patentable weight. MPEP 2111.02(II) states that "If the body of a claim fully and intrinsically sets forth all of the limitations of the

claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction". Here, the body of the claim sets forth all the steps and starting materials, and the preamble of the claim merely sets forth an intended use of the steps.

20. For reasons stated above the claims were prima facie obvious over the prior art.

21. The rejection of claims 15-18, 22, and 24-26 under 35 U.S.C. 103(a) as being unpatentable over Wettstein et al., (1999), Vollenweider et al (1998), Bowden (2001) and Perry et al. (2001), in view of Greibel et al. (2001), is being applied to the amended claims for reasons of record in the Office Action dated 16 August 2010.

22. The teachings of Wettstein et al., Vollenweider et al, Bowden and Perry et al. are set forth above.

23. Wettstein et al., Vollenweider et al. Bowden or Perry et al. do not teach further administration of a compound selected from levocobastine, SR48692 and SR142948.

24. Griebel et al teach that intraperitoneal administration of NT1 receptor antagonist SR48692 in rodent models results in effectively treating generalized anxiety disorders (Figure 4; abstract; page 624, col 2, para 2).

25. Applicant argues that Griebel does not remedy the deficiency of the foregoing reference. Applicant also argues that Griebel teaches that NT1 is effective in certain types of anxiety, suggesting that NT1 is ineffective in general anxiety disorder. Applicant therefore, requests the rejection to be withdrawn.

26. Applicant's arguments are fully considered however, are not found to be

persuasive. Firstly, the foregoing references clearly render the claimed invention obvious for reasons stated above. Secondly, the claims broadly recite "an anxiety disorder" not a specific anxiety disorder. It is noted that USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). The rejection is therefore, maintained.

Conclusion

27. No claims are allowed.

28. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

29. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ali Salimi, can be reached on (571) 272-0909. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/A. D./
Examiner, Art Unit 1649
22 April 2011

/DANIEL E. KOLKER/

Primary Examiner, Art Unit 1649

April 26, 2011